FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 101195-65

U S APPLICATION NO (IF KNOWN, SEE 37 CFR): TBA 10/019452

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/02062	9 March 2000 (09.03.00)	9 March 1999 (09.03.99)

TITLE OF INVENTION

Therapy and Use of Compounds in Therapy

APPLICANT(S) FOR DO/EO/US

Stefan Anker; Andres Coates; Hans-Dieter Volk; Ralf Reiner Schumann; Mathias Plauth

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31)
5. ☐ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409)
12. ☐ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Petition for Revival of an International Application for Patent Designating the U.S. Abandone Unintentionally Under 37 CFR 1.137(b)

U.S. APPLICATION NO (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/TBA 019452	PCT/EP00/02062	101195-65

24. The following fees are submitted..		CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :			
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$1040.00**		
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	**$890.00**		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$740.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$710.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =		**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		**$130.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	23 - 20 =	3	x $18.00	**$54.00**	
Independent claims	1 - 3 =	0	x $84.00	**$0.00**	
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$1,074.00**	
☒ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				**$537.00**	
SUBTOTAL =				**$537.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**	
TOTAL NATIONAL FEE =				**$537.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**	
TOTAL FEES ENCLOSED =				**$537.00**	
				Amount to be: refunded	$
				charged	$

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **14-1263** in the amount of **$537.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **14-1263** A duplicate copy of this sheet is enclosed.

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NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

correspondence address associated with Customer No. 27387

SIGNATURE

Bruce S. Londa

NAME

33,531

REGISTRATION NUMBER

October 18, 2001

DATE

10/019452

JC13 Rec'd PCT/PTO 19 OCT 2001

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): **Stefan Anker et al.**			Docket No. **101195-65**
Serial No. **TBA**	Filing Date **Concurrently Herewith**	Examiner **TBA**	Group Art Unit **TBA**

Invention: **Therapy and Use of Compounds in Therapy**

I hereby certify that the following correspondence:

U.S. National stage appln of PCT/EP00/02062 and Petition to revive; preliminary amendment

(Identify type of correspondence)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231 on

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P06A/REV02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Atty's Docket No. 101195-65

APPLICANT : Stefan Anker et al.

FILED : Concurrently Herewith

FOR : Therapy and Use of Compounds in Therapy

PRELIMINARY AMENDMENT

Hon. Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to examination, please amend the application as follows:

IN THE CLAIMS

Please amend the claims in accordance with the attached marked-up pages. A clean copy of the amended claims is also enclosed.

REMARKS

The above amendments were made to place the claims into proper United States Patent Format.

Respectfully Submitted,

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Amended Claims - Marked-Up Copy

1. A method of treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chronic *renal* failure, diabetes, rheumatoid arthritis in a patient the method comprising administering to the *patient* an effective amount of a compound that is able to reduce the production, *absorption and/or* the effect of an endotoxin (lipopolysaccharide; LPS).

2. (amended) A method ~~of~~ according to claim 1, further treating, preventing or ameliorating endotoxin-mediated immune activation in body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chromic renal failure, diabetes, rheumatoid arthritis the method comprising administering to the patient an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; LPS).

3. (amended) A method according to claim 1 ~~and 2~~ wherein the compound is able to bind to an endotoxin (lipopolysaccharide; LPS) molecule.

4. (amended) A method according to claim 1 ~~to 3~~ wherein the compound is able to reduce *the* available endotoxin in the patient.

Amended Claims - Marked-Up Copy

5. (amended) A method according to claim 1 ~~to 4~~ wherein the compound is a bile acid.

6. (amended) A method according to claim 1 ~~to 4~~ wherein the bile acid is any one of ursodesoxycholic acid, chemodeoxycholic acid, dehydrocholic acid, cholic acid and deoxycholic acid.

7. (amended) A method according to claim 1 ~~to 4~~ wherein the compound is LPS binding protein.

8. (amended) A method according to claim 1 ~~to 4~~ wherein the compound is bactericidal/permeability increasing protein (BPI).

9. (amended) A method according to claim 1 ~~to 4~~ wherein the compound is, a lipoprotein, for instance, low densitiy lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL), apolipoprotein (a), a lipoprotein mixture.

10. (amended) A method according to claim 1 ~~to 4~~ wherein the treatment is a combination of a compound according claim 7 and claim 9.

Amended Claims - Marked-Up Copy

11. (amended) A method according to claim 1 ~~to 4~~ wherein the compound is or an antibody capable of binding to endotoxin (lipopolysaccharide; LPS).

12. (amended) A method according to claim 1 ~~to 4~~ wherein the compound is or an antibody capable of binding to endotoxin (lipopolysaccharide; LPS).

13. (amended) A method according to claim 1 ~~to 4~~ wherein the compound is an antibody able to bind to the CD14 receptor.

14. (amended) A method according to claim 1 ~~to 4~~ wherein the compound is a soluble CD 14 receptor.

15. (amended) A method according to claim 1 ~~to 4~~ wherein the compound is a drug blocking effectively signaling through toll-like receptors, for instance toll-like receptor 4 and toll-like receptor 2.

16. (amended) A method according to claim 1 ~~to 4~~ wherein the compound is colostrum of human, bovine, or other mamallian origin.

Amended Claims - Marked-Up Copy

17. (amended) A method according to claim 1 ~~to 4~~ wherein the compound is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS).

18. (amended) A method according to claim 1 ~~to 4, and 17~~ wherein the compound is able to decrease the cytokine production by a cell in response to endotoxin (lipopolysaccharide; LPS).

19. (amended) A method according to claim 1~~, 2 and 17, and 18~~ wherein the compound is a compound named in claim 5 to 16.

20. (amended) A method according to ~~any one of the preceding claims~~ claim 1 wherein the compound is administered orally.

21. (amended) A method according to ~~any one of the preceding claims~~ claim 1 wherein the compound is administered intravenously.

22. (amended) A method according to ~~any one of the preceding claims~~ claim 1 wherein the compound is administered rectally.

~~23. The combined application of any method or use of any of the preceding claims in an individual patient.~~

Amended Claims - Clean Copy

1. A method of treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chronic *renal* failure, diabetes, rheumatoid arthritis in a patient the method comprising administering to the *patient* an effective amount of a compound that is able to reduce the production, *absorption and/or* the effect of an endotoxin (lipopolysaccharide; LPS).

2.(amended) A method according to claim 1, further treating, preventing or ameliorating endotoxin-mediated immune activation in body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chromic renal failure, diabetes, rheumatoid arthritis the method comprising administering to the patient an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; LPS).

3.(amended) A method according to claim 1 wherein the compound is able to bind to an endotoxin (lipopolysaccharide; LPS) molecule.

4.(amended) A method according to claim 1 wherein the compound is able to reduce *the* available endotoxin in the patient.

Amended Claims - Clean Copy

5.(amended) A method according to claim 1 wherein the compound is a bile acid.

6.(amended) A method according to claim 1 wherein the bile acid is any one of ursodesoxycholic acid, chemodeoxycholic acid, dehydrocholic acid, cholic acid and deoxycholic acid.

7.(amended) A method according to claim 1 wherein the compound is LPS binding protein.

8.(amended) A method according to claim 1 wherein the compound is bactericidal/permeability increasing protein (BPI).

9.(amended) A method according to claim 1 wherein the compound is, a lipoprotein, for instance, low densitiy lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL), apolipoprotein (a), a lipoprotein mixture.

10.(amended) A method according to claim 1 wherein the treatment is a combination of a compound according claim 7 and claim 9.

Amended Claims - Clean Copy

11.(amended) A method according to claim 1 wherein the compound is or an antibody capable of binding to endotoxin (lipopolysaccharide; LPS).

12.(amended) A method according to claim 1 wherein the compound is or an antibody capable of binding to endotoxin (lipopolysaccharide; LPS).

13.(amended) A method according to claim 1 wherein the compound is an antibody able to bind to the CD14 receptor.

14.(amended) A method according to claim 1 wherein the compound is a soluble CD 14 receptor.

15. (amended) A method according to claim 1 wherein the compound is a drug blocking effectively signaling through toll-like receptors, for instance toll-like receptor 4 and toll-like receptor 2.

16.(amended) A method according to claim 1 wherein the compound is colostrum of human, bovine, or other mamallian origin.

Amended Claims - Clean Copy

17. (amended) A method according to claim 1 wherein the compound is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS).

18. (amended) A method according to claim 1 wherein the compound is able to decrease the cytokine production by a cell in response to endotoxin (lipopolysaccharide; LPS).

19. (amended) A method according to claim 1 wherein the compound is a compound named in claim 5 to 16.

20. (amended) A method according to claim 1 wherein the compound is administered orally.

21. (amended) A method according to claim 1 wherein the compound is administered intravenously.

22. (amended) A method according to claim 1 wherein the compound is administered rectally.

THERAPY AND USE OF COMPOUNDS IN THERAPY

The present invention relates to therapy and the use of agents in the therapy of cachexia and wasting syndromes due to diseases other than congestive heart failure. Cachexia occurs in a number of other chronic diseases, like liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis. Cachexia and weight loss are linked to inflammatory processes and they are linked to increased mortality and/or morbidity. Cytokine activation is a potential causal mechanism for the development of cachexia also in these other diseases.

No one has previously proposed that one or all of the following agents may be useful in the management of patients with cachexia due to liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis:

- a bile acid,
- BPI,
- LPS binding protein or a functional equivalent thereof
- an antibody capable of binding to endotoxin,
- the combination of lipoproteins and LPS binding protein
- activated charcoal, Fuller's earth, attapulgite, kaolin or bentonite or a clay,
- an antibody able to bind the CD14 receptor,
- a soluble CD14 receptor,
- a drug blocking effectively signaling through toll-like receptors, particularly toll-like receptor 4 and 2
- colostrum of human, bovine, or other mamallian origin

The following classes of patients in particular may benefit from treatment

1. Patients with liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis.

2. Patients with cachexia due to liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis.

It is preferred that the patient has cachexia, as characterised by loss of muscle, fat, and or bone tissue.

It is preferred that the patient has experienced weight loss >7.5%.

It is preferred that the compound is able to substantially reduce the biological activity of endotoxin (lipopolysaccharide) such that the endotoxin mediated production of inflammatory cytokines in the circulating blood is reduced..

By "bile acid" we include all naturally occurring bile acids whether from man or from another animal. Also is included bile acids which are synthetic or semi-synthetic derivatives of naturally occurring bile acids. Of course, all bile acids including those that are "naturally occurring" may be synthesised chemically.

Bile acids are available from Falk Pharma GmbH and are described, for example, in WP96/17859, DE29717252 and WO98/05339.

Bile acids for use in the method of the invention include, but are not limited to, chemodeoxycholic acid (3α, 7α - dihydroxy-5-cholan-24-oic acid), arsodeoxycholic acid (3α, 7-dihydroxy-5-cholan-24-oic acid), dehydrocholic acid (3,7,12-trioxo-5-cholan-24-oic acid), cholic acid and deoxycholic acid.

Preferably, the bile acid is a bile acid which is able to form micelles. Preferably, the bile acid is able to form a micelle around an endotoxin (lipopolysacharide molecule). It is particularly preferred that the bile acid is able to bind to endotoxin (lipopolysaccharide) molecules and substantially reduce the available endotoxin in the patient. In particular, it is preferred if the bile acid is able to substantially reduce the biological activity of endotoxin (lipopolysaccharide) such that the endotoxin has a substantially reduced effect on the liver or does not reach the liver in a substantially active form.

It is preferred if the bile acid is any one of ursodeoxycholic acid, chemodeoxycholic acid, dehydrocholic acid, cholic acid and deoxycholic acid.

It is preferred if the bile acid is ursodeoxycholic acid.

Originally, UDCA was registered for the medical treatment of gallstones (Leuschner et al. Our ten year experience in gallstone dissolution. Comparison with the national Canadian gallstone (NCGS, USA) and the Toky co-operative gallstone study (TCGS, Japan). Gastroenterology 1982, 82:1113). Ursodeoxycholic acid has for many years been proposed to be useful also in patients with cholestatic disease, and particularly in patients with primary biliary cirrhosis, a chronic cholestatic liver disease (Lindor et al. Effects of ursodeoxycholic acid on survival in patients with primary biliary cirrhosis. Gastroenterology 1996, 110:1515-1518). In analogy, UDCA is used in other cholestatic disorders like primary sclerosing cholangitis (Beuerset al: Therapie der autoimmunen Hepatitis, primär biliären Zirrhose und primär sklerosierenden Cholangitis. Konsensus der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten. Z. Gastroenterologie 1997; 35:1041-1049) or benign cholestasis of pregnancy (Palma et al. Ursodeoxycholic acid in the treatment of cholestasis of pregnancy: a randomized, double-blind study controlled with placebo. J Hepatol 1997, 27:1022-1028). Regarding its mode of action, most authorities regard increased bile flow and a reduced hepatocellular insult as a result of improved bile flow and altered bile salt patterns as the main modes of UDCA action in chronic cholestatic liver diseases.

However, a very recent meta-analysis concluded that "Published randomised controlled trials of UDCA do not show evidence of therapeutic benefit in primary biliary cirrhosis and its use as standard therapy needs to be re-examined." (Goulis et al. Randomised controlled trials of ursodeoxycholic-acid therapy for primary biliary cirrhosis: a meta-analysis. Lancet 1999 Sep 25;354:1053-1060.)

As for other liver diseases another recent review article concluded "Ursodeoxycholic acid is of unproven efficacy in non-cholestatic disorders such as acute rejection after liver transplantation, non-alcoholic steatohepatitis, alcoholic liver disease and chronic viral hepatitis." Trauner M and Graziadei IW. Review article: mechanisms of action and

therapeutic applications of ursodeoxycholic acid in chronic liver diseases. Aliment Pharmacol Ther. 1999 Aug; 13(8): 979-996.

Therefore, treatment with ursodeoxycholic acid (UDCA) can not be considered a treatment with proven efficacy in patients with liver disease.

It has never been suggested that ursodeoxycholic acid (UDCA) should be specifically given to patients with cachexia due to liver cirrhosis.

It has never been suggested that ursodeoxycholic acid (UDCA) should be specifically given to patients with alcoholic liver cirrhosis. In fact, such patients were specifically excluded from studies.

Alterations in nutritional state leading to abnormal body composition are detectable already in early stages of liver cirrhosis and are clinically overt in the great majority of patients with advanced disease. Despite the well accepted prognostic role of cachexia or protein-energy-malnutrition in cirrhosis its pathogenesis is not fully understood. Although alcohol abuse and inadequate nutrient composition may play some role in patients with alcoholic liver disease this clearly is not operative in patients with liver disease of other etiology in whom malnutrition is as great a problem as in those with alcoholic liver disease (Plauth et al: ESPEN guidelines for nutrition in liver disease and transplantation. Clin Nutr 1997, 16:43-55). Nutrient intake is reduced in many patients with advanced liver cirrhosis and does not match requirements. It is unknown, however, whether food intake is reduced as a consequence of mechanical factors such as ascites or due to altered appetite regulation or other processes.

It is long known that endotoxaemia occurs in a number of patients with liver cirrhosis. It is not known, whether endotoxin (LPS) levels are particularly raised in patients with cachexia due to liver cirrhosis.

Depending of the severity of the liver cirrhosis process, cachexia occurs in 30 to 60% of patients with liver cirrhosis, and the survival of patients with cachexia in liver cirrhosis is impaired . (Plauth et al: ESPEN guidelines for nutrition in liver disease and transplantation.

Clin Nutr 1997, 16:43-55). There is no known specific therapy for these patients, and randomised placebo controlled clinical trials to reverse the cachexia in liver cirrhosis patients, and particularly in those with alcohol induced liver cirrhosis have not been performed. Additionally, patients with a body cell mass (BCM) < 35% of body weight have reduced survival also after liver transplantation, and the 5-year survival rate is 54% compared to 88% in patients with BCM >35% ($p < .01$) (Selberg et al. Identification of high- and low-risk patients before liver transplantation: a prospective cohort study of nutritional and metabolic parameters in 150 patients. Hepatology 1997;25:652-657).

It has also been suggested that bile acids can protect the liver against endotoxin action in obstructive jaundice when patients undergo surgery (Greve et al. Bile acids inhibit endotoxin-induced release of tumor necrosis factor by monocytes: an in vitro study. Hepatology 1989 Oct;10(4):454-458). With regards to monocyte generated cytokine production in response to LPS, in this study deoxycholic acid was the most effective, chenodeoxycholic acid was less effective and ursodeoxycholic acid was ineffective in the concentrations used. Bile acids did not inactivate endotoxin as measured in a chromogenic Limulus amebocyte lysate assay. In these studies patients with non-cholestatic or alcoholic aetiology were not considered, and there was no data or discussion of cachexia and weight loss.

In experiments, rats with obstructive jaundice, LPS was administered via the portal vein. In UDCA-treated rats, the endotoxin concentration was significantly lower, however, that UDCA had no effect on the TNF-alpha levels (Hori Y & Ohyanagi H. Protective effect of the intravenous administration of ursodeoxycholic acid against endotoxaemia in rats with obstructive jaundice. Surg-Today 1997;27:140-144). In a case control study UDCA showed also no clinical benefit in patients with chronic hepatitis C, and serum TNF and IL-6 levels could not be shown to be affected by UDCA treatment (Lu et al. Efficacy of ursodeoxycholic acid in the treatment of patients with chronic hepatitis C. J Gastroenterol Hepatol 1995;10:432-437.

In summary, the immunological effects of ursodeoxycholic acid (UDCA) on plasma LPS and cytokine levels are poor in these studies, and the cellular effects of ursodeoxycholic acid (UDCA) are conflicting.

It is important to note that it has never been proposed that ursodeoxycholic acid (UDCA) should be given in patients with weight loss, i.e. cachexia, in patients with liver disease. It has never been proposed that ursodeoxycholic acid (UDCA) could prevent or reverse weight loss, i.e. cachexia, in patients with liver disease. Additionally, it has never been proposed that ursodeoxycholic acid (UDCA) could prevent or reverse weight loss, i.e. cachexia, in patients with chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis.

The invention will now be described by reference to the following additional examples and figures.

Example 1:

We have tested the ability of ursodeoxycholic acid (UDCA, FALK Pharma GmbH) and BPi to inhibit LPS-mediated TNF production in whole blood of patients with cachexia.

We studied 4 patients with cachexia due to liver cirrhosis. The patients had all weight loss >7.5% compared to their previous normal weight. In 3 of the 4 patients had a alcoholic aetiology. All patients were studied twice on 2 subsequent days (day "-1" and day "0"), see Figure 9 to 12.

Methods: Heparinized whole blood was diluted 1:10 with medium +/- LPS (50 pg/ml), +/- BPI (1 µg/ml), and +/- UDCA (1 µg/ml – 1 mg/ml) according to the manufactorer's recommendation (Milenia whole blood assay ; DPC Biermann, Bad Nauheim, Germany) and incubated for 4 hours at 37°C. In the supernatant, we assessed concentrations of TNF and IL-6 using the semiautomated Immulite system (DPC-Biermann, Bad Nauheim, Germany).

Results: In patients with cachexia due to liver cirrhosis spontaneous ("Control" data) and LPS-stimulated production of TNF and IL6 is significantly elevated compared to that of healthy subjects. LPS-stimulated cytokine production was inhibited by UDCA independently of the effects of the ethanol solution. The detailed results are presented in Figure 9 to 12. 1mg/ml UDCA reduced LPS-stimulated TNF production on average by >99% and IL6 production by 97% (ethanol 1% alone on average only by 38% for TNF and 43% for IL6). 100 µg/ml UDCA reduced LPS-stimulated TNF and IL6 production by 42% and 13%, respectively, ethanol 0.1% alone on average only 9% for TNF and IL6 production increased by 18% for ethanol alone).

BPi (1 µg/ml) reduced significantly the spontaneous production of TNF and IL6 of whole blood of patients with cachexia due to liver cirrhosis. In 8 experiments 6 times TNF and IL6 levels, respectively, were lowered by at least 5 pg/ml or towards non-detectability, and only in 2 cases TNF and IL6 levels remained stable ($p<0.05$ for changes).

Conclusion: This is the first documentation that LPS-stimulated cytokine production of whole blood of patients with cachexia can be inhibited by in vitro application of ursodeoxycholic acid (UDCA). This is the first documentation that spontaneous production of inflammatory cytokines in whole blood of patients with cachexia can be inhibited by application of BPi in vitro.

Example 2:

We have tested the ability of the therapeutic application of ursodeoxycholic acid (UDCA, FALK Pharma GmbH) to lower plasma levels of TNF and IL6 and to lower spontaneous and LPS-stimulated whole blood cytokine production in patients with cachexia.

We studied in 2 patients with cachexia due to liver cirrhosis plasma cytokine levels after treatment with 3 times 250 mg daily UDCA (FALK Pharma GmbH). The patients had weight loss >7.5% compared to their previous normal weight. The patients were studied at baseline prior to the treatment on 2 subsequent days (day "-1" and day "0"), and then they were restudied on day 1 ("1"), day 2 ("2"), and day 5 ("5"), see Figure 9 and 12.

Methods: Heparinized whole blood was diluted 1:10 with medium +/- LPS (50 pg/ml), +/- BPI (1 µg/ml), and +/- UDCA (1 µg/ml – 1 mg/ml) according to the manufactorer's recommendation (Milenia whole blood assay ; DPC Biermann, Bad Nauheim, Germany) and incubated for 4 hours at 37°C. In the supernatant and in plasma, we assessed concentrations of TNF and IL-6 using the semiautomated Immulite system (DPC-Biermann, Bad Nauheim, Germany).

Results: Only patient 1 showed elevated plasma levels at baseline (Figure 9). During 5 days of treatment plasma levels of TNF were lower. In patient 4 we were able to reassess whole blood TNF and IL6 production after 1 and 2 days of treatment with UDCA. Spontaneous production of TNF and IL6 in whole blood was reduced substantially to almost undetectable levels. After 2 days of UDCA treatment LPS-stimulated cytokine production was found to be lowered by 43.5% for TNF and by 39.6% for IL6.

Conclusion: This is the first documentation that LPS-stimulated cytokine production of whole blood of patients with cachexia can be inhibited by in vivo therapeutic application of

ursodeoxycholic acid (UDCA). This is the first documentation that plasma levels of TNF alpha of patients with cachexia can be inhibited by application of BPi.

Example 3: Endotoxin in cachectic patients with liver cirrhosis.

It has never been studied, whether endotoxin (LPS) or a marker of endotoxaemia may be raised in patients with liver cirrhosis who suffer from cachexia. Plasma levels of soluble CD14 (sCD14) can reflect the history of LPS – cell interaction (Anker et al,., Am J Cardiol 1997; ;79:1426-1430.).

We investigated in 46 patients with liver cirrhosis (54±12 years, female 15, male 31, Child A:B:C=24:13:9), alcoholic aetiology in 32 patients) resting energy expenditure (REE, indirect calorimetry), food intake diaries, fat mass (skin fold thickness and calculation according to standard formulae) and body cell mass (BCM, body impedance, Data Input 2000, USA). Soluble CD14 was measured by ELISA (R&D Systems). The majority of patients had a BCM of <35% of body weight (mean±standard deviation: 25±7%, median 33%, range 11.8 – 41.9%). Plasma sCD14 levels were significantly increased in patients (mean±standard deviation: 4045±623 pg/ml, median 3920 pg/ml, range 2960 – 5460 pg/ml) compared to sCD14 levels of healthy individuals (mean: 2714 pg/ml, upper limit of normal 3711 pg/ml, as published in Anker et al,., Am J Cardiol 1997; ;79:1426-1430).

The patients with low BCM relative to their body weight must be considered to suffer from wasting disease, which was the majority in this study (63%of patients had a BCM <35%/kg body weight). The majority of patients in this study were metabolically catabolic as evidenced by a REE/BCM coefficient of 67±19 kcal/kg BCM (range 43 – 163, normal range in healthy subjects: 45 – 55 kcal/kg).

The strongest correlation that we found was between the degree of wasting (BCM per kg body weight) and the marker of endotoxaemia, i.e. soluble CD14 ($r=-0.565$, $p<0.001$). This means, the lower the relative BCM (i.e. the more cachectic) a patient was the higher the were also the sCD14 plasma levels. Plasma levels of sCD14 also correlated closely and directly with the degree of catabolic energetic/metabolic status (i.e. the REE/ BCM coefficient), $r=0.549$, $p<0.001$.

Conclusion: This is the first study suggesting that endotoxin (LPS) levels in patients with liver cirrhosis may be particularly high in patients with cachexia. This study also suggests that endotoxin (LPS) is causally related to the characteristics of the cachexia syndrome in liver cirrhosis, i.e. reductions in muscle tissue and increases in metabolic rate.

Example 4: LBP in cachectic patients due to liver cirrhosis.

We have studied LBP plasma levels in 6 patients with cachexia due to liver cirrhosis. The patients had weight loss >7.5% compared to their previous normal weight. The disease aetiology was thought to be alcoholic in 4 cases and non-alcoholic in 2 cases. In non of these patients increased LBP levels were found (all below 20 µg/ml). High levels LBP can (together with lipoproteins) block LPS mediated production of inflammatory cytokines. We conclude that LBP is lacking in patients with cachexia due to liver cirrhosis, and that the application of LBP, possibly together with lipoproteins, could counteract the inflammatory status seen in these patients.

CLAIMS

1. A method of treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis in a patient the method comprising administering to the patient an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; LPS).

2. A method of treating, preventing or ameliorating endotoxin-mediated immune activation in body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis the method comprising administering to the patient an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; LPS).

3. A method according to claim 1 and 2 wherein the compound is able to bind to an endotoxin (lipopolysaccharide; LPS) molecule.

4. A method according to claim 1 to 3 wherein the compound is able to reduce the available endotoxin in the patient.

5. A method according to claim 1 to 4 wherein the compound is a bile acid.

6. A method according to claim 1 to 4 wherein the bile acid is any one of ursodesoxycholic acid, chemodeoxycholic acid, dehydrocholic acid, cholic acid and deoxycholic acid.

7. A method according to claim 1 to 4 wherein the compound is LPS binding protein.

8. A method according to claim 1 to 4 wherein the compound is bactericidal/permeability increasing protein (BPI).

9. A method according to claim 1 to 4 wherein the compound is, a lipoprotein, for instance, low densitiy lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL), apolipoprotein (a), a lipoprotein mixture.

10. A method according to claim 1 to 4 wherein the treatment is a combination of a compound according claim 7 and claim 9.

11. A method according to claim 1 to 4 wherein the compound is or an antibody capable of binding to endotoxin (lipopolysaccharide; LPS).

12. A method according to claim 1 to 4 wherein the compound is or an antibody capable of binding to endotoxin (lipopolysaccharide; LPS).

13. A method according to claim 1 to 4 wherein the compound is an antibody able to bind to the CD14 receptor.

14. A method according to claim 1 to 4 wherein the compound is a soluble CD14 receptor.

15. A method according to claim 1 to 4 wherein the compound is a drug blocking effectively signaling through toll-like receptors, for instance toll-like receptor 4 and toll-like receptor 2.

16. A method according to claim 1 to 4 wherein the compound is colostrum of human, bovine, or other mamallian origin.

17. A method according to claim 1 to 4 wherein the compound is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS).

18. A method according to claim 1 to 4, and 17 wherein the compound is able to decrease the cytokine production by a cell in response to endotoxin (lipopolysaccharide; LPS).

19. A method according to claim 1, 2 and 17, and 18 wherein the compound is a compound named in claim 5 to 16.

20. A method according to any one of the preceding claims wherein the compound is administered orally.

21. A method according to any one of the preceding claims wherein the compound is administered intravenously.

22. A method according to any one of the preceding claims wherein the compound is administered rectally.

23. The combined application of any method or use of any of the preceding claims in an individual patient.

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(54) Title: THERAPY AND USE OF COMPOUNDS IN THERAPY

(57) Abstract

The present invention relates to therapy and the use of agents in the therapy of cachexia and wasting syndromes due to diseases other than congestive heart failure. Cachexia occurs in a number of other chronic diseases, like liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis. Cachexia and weight loss are linked to inflammatory processes and they are linked to increased mortality and/or morbidity. Cytokine activation is a potential causal mechanism for the development of cachexia also in these other diseases. The invention describes a method of treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis in a patient. The method comprises administering to the patient an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; LPS). The invention describes also a method of treating, preventing or ameliorating endotoxin–mediated immune activation in body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis. The method comprises administering to the patient an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; LPS).

Figure 1:

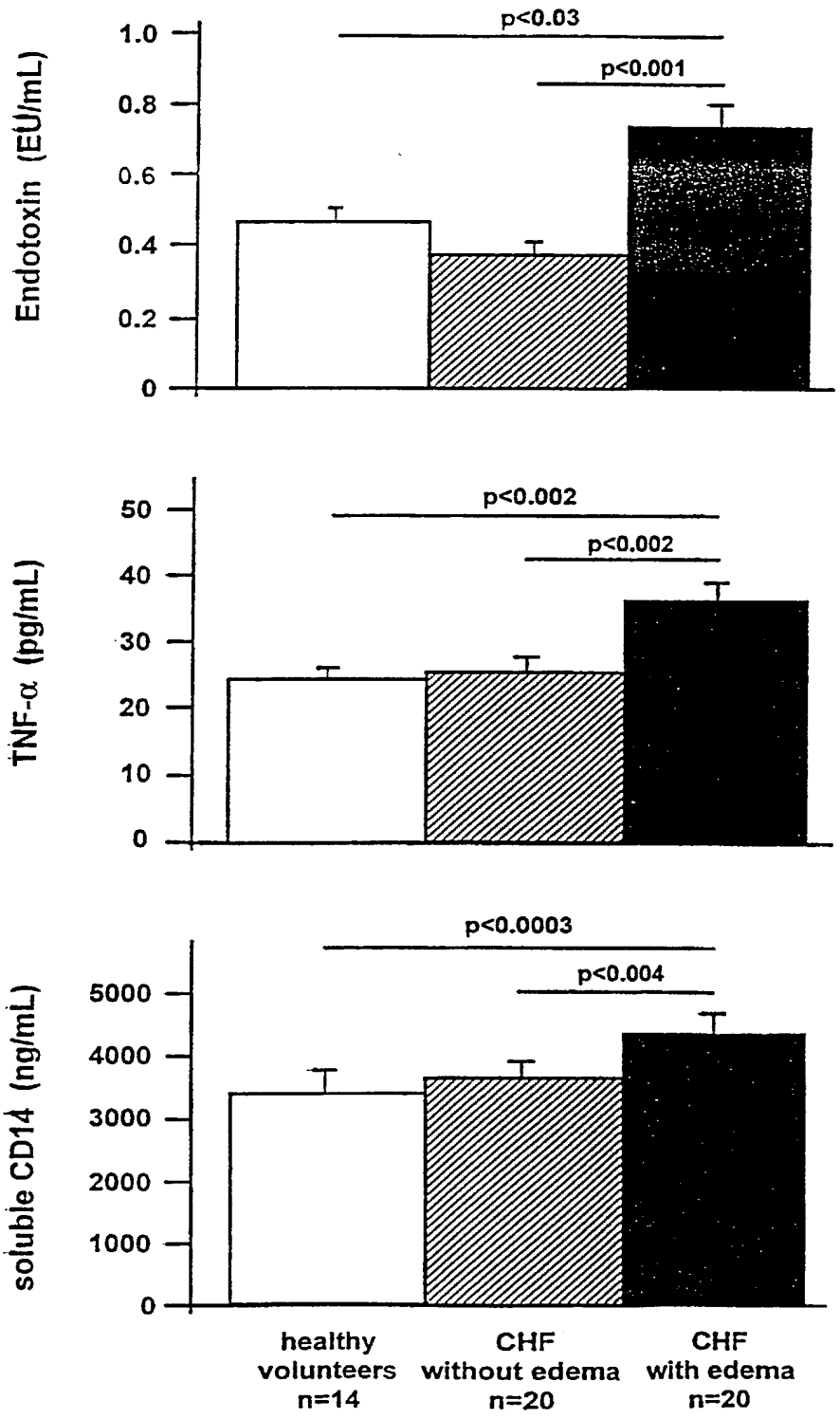
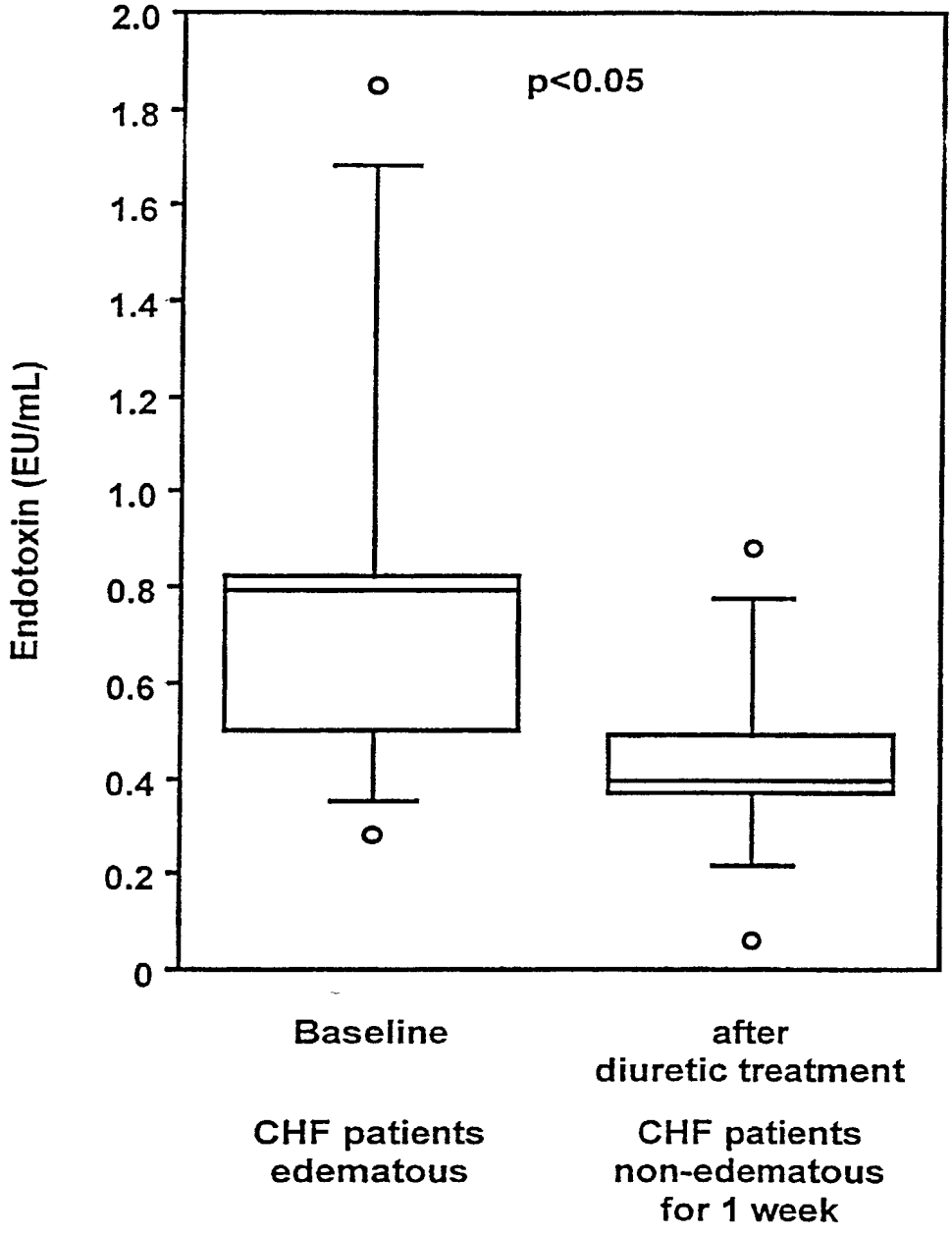

p<0.03
p<0.001
Endotoxin (EU/mL)
1.0
0.8
0.6
0.4
0.2
0
p<0.002
p<0.002
TNF-α (pg/mL)
50
40
30
20
10
0
p<0.0003
p<0.004
soluble CD14 (ng/mL)
5000
4000
3000
2000
1000
0
healthy volunteers n=14
CHF without edema n=20
CHF with edema n=20

Figure 2:


2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
Endotoxin (EU/mL)
p<0.05
Baseline
after diuretic treatment
CHF patients edematous
CHF patients non-edematous for 1 week

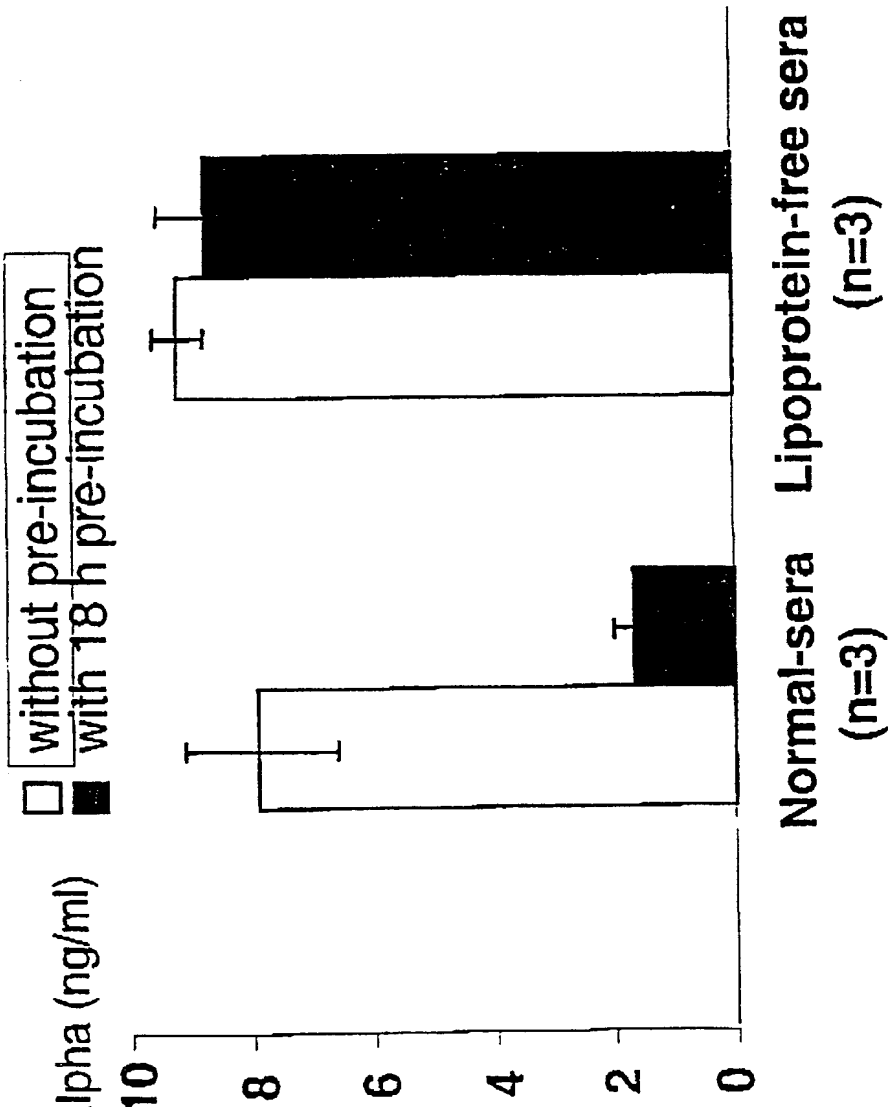


Figure 3: Lipoprotein-free serum lacks LPS-neutralizing activity

Sera were incubated with 3 ng/ml LPS and added to human monocytes directly or after a 18 h pre-incubation time

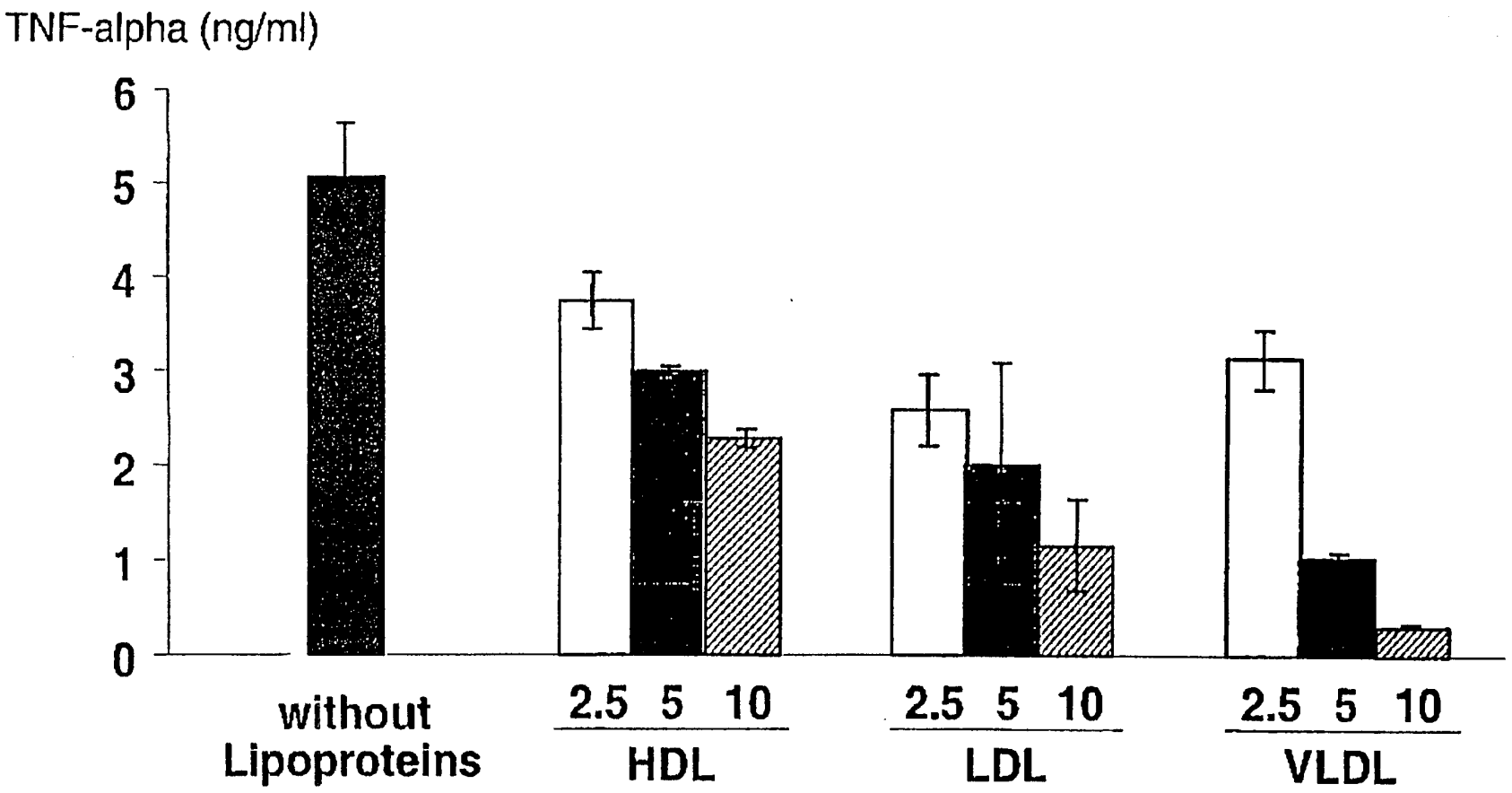


Figure 4: Lipoproteins including HDL, LDL and VLDL inhibit LPS-induced TNF-release of monocytes. The effects of LDL and VLDL are even stronger than that of HDL.
In all experiments: n=3
Lipoproteins were added to Lipoprotein-free Serum (5 %) and incubated for 17 h with 3 ng/ml LPS before addition to monocytes

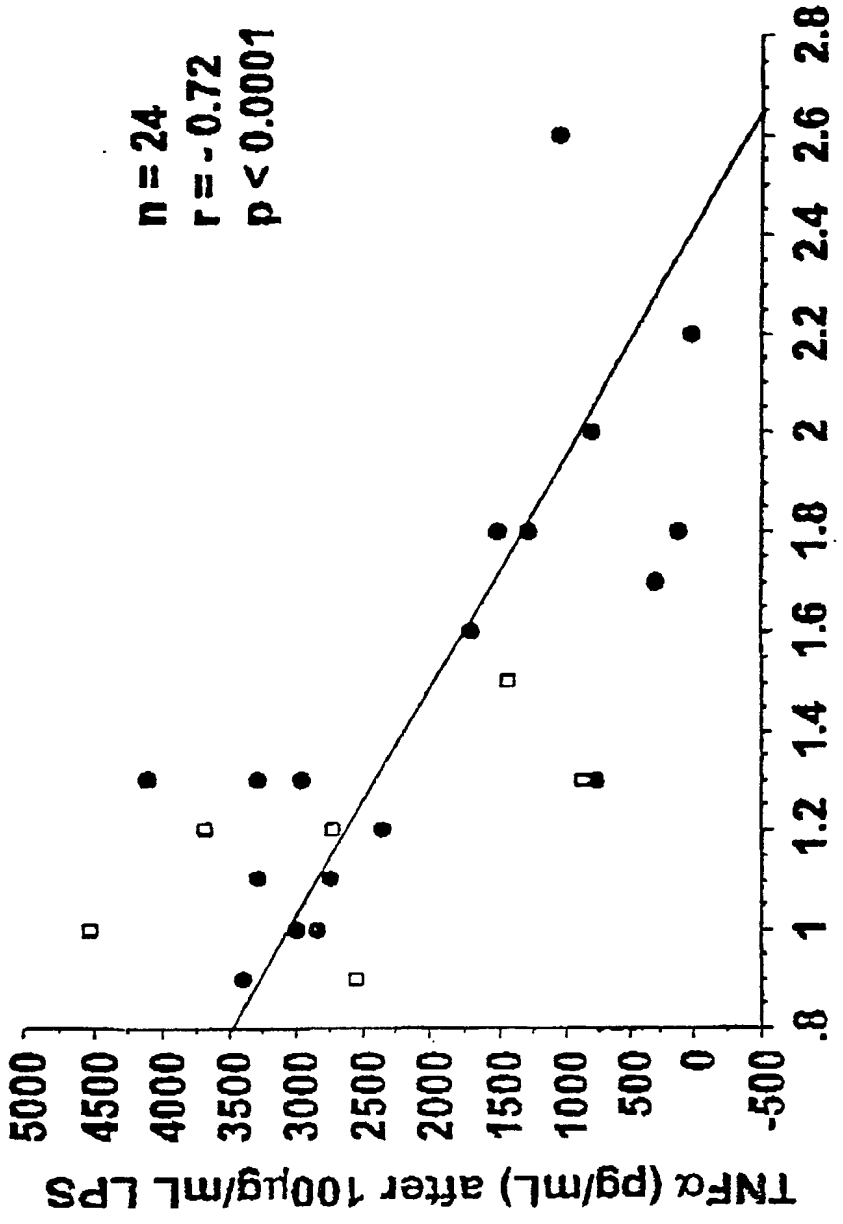


Figure 5: Whole Blood Analysis

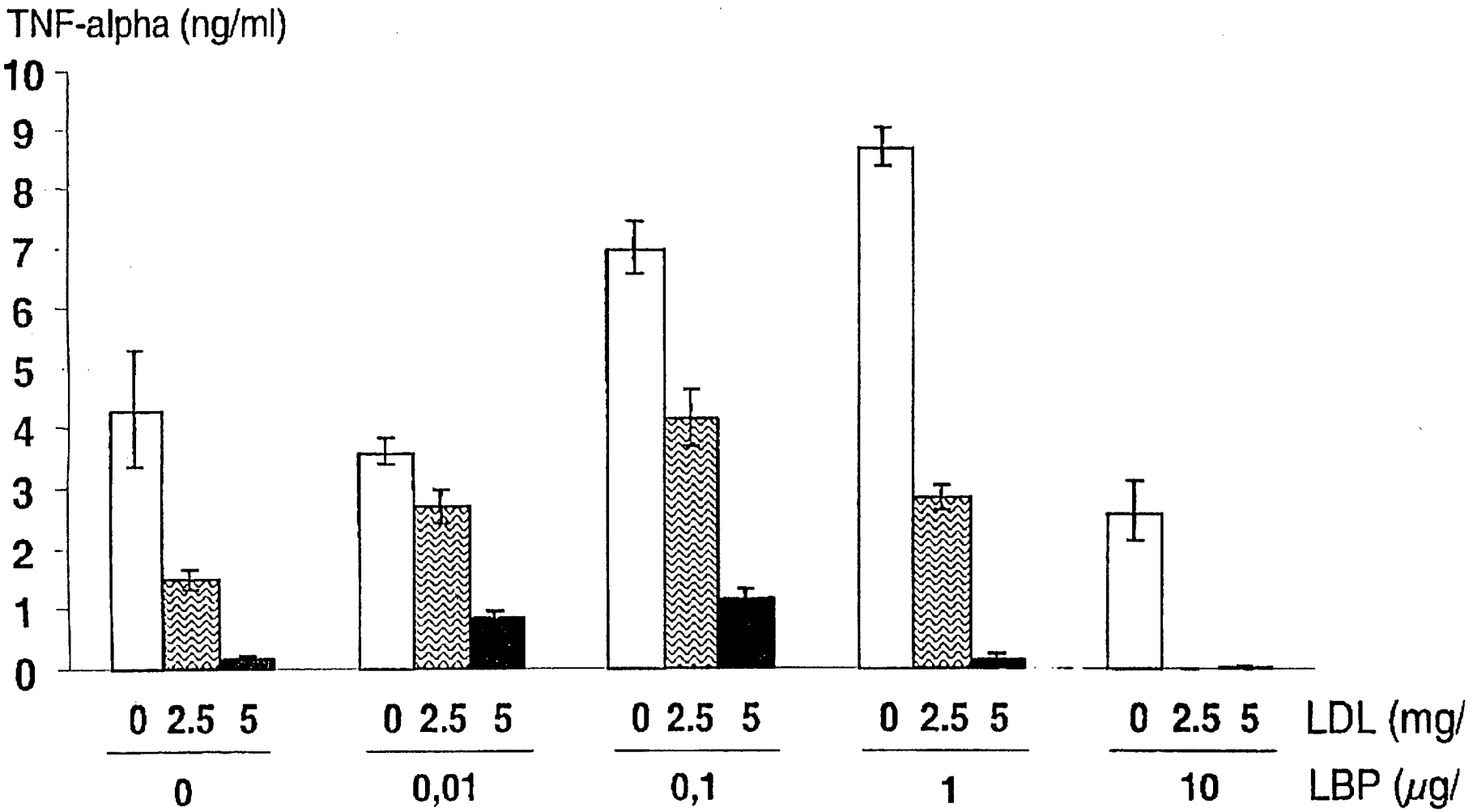


Figure 6: In the presence of elevated LBP-concentrations lipoproteins show emhanced LPS-neutralization capacity. In all experiments: n=3.
LBP and LDL were pre-incubated for 17 h before cell stimulation with 3 ng/ml LPS

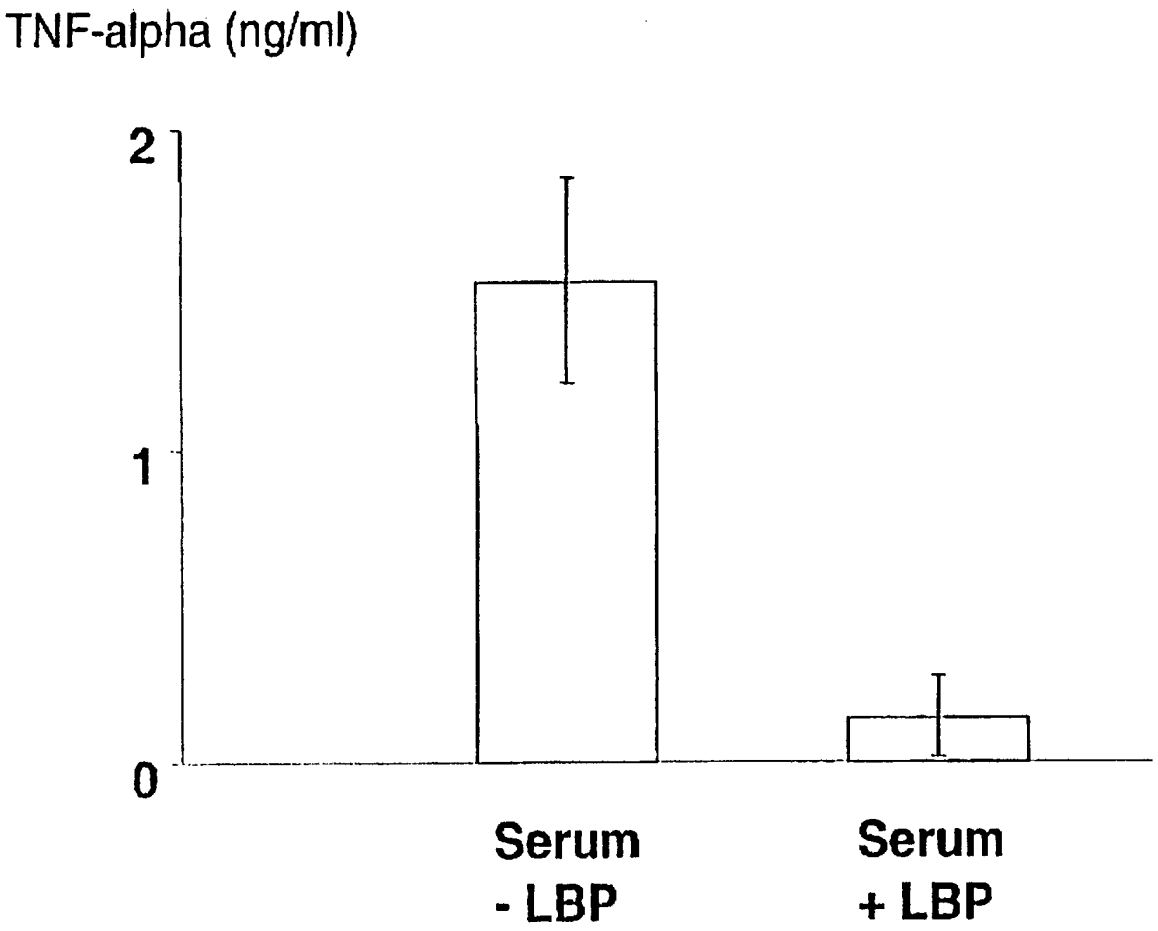


Figure 7: Addition of LBP to lipoprotein containing serum reduces LPS-mediated TNF production (n=3).

Normal serum +/- 10 µg/ml LBP was incubated with 3 ng/ml LPS for 16 h, and then added to monocytes

Figure 8: LPS - Neutralisation by UDCA in whole blood of 4 healthy subjects

Measurements by Immulite	Control D		Control J		Control Ch		Control F	
	TNF	IL6	TNFα	IL6	TNFα	IL6	TNFα	IL6
	pg/ml		pg/ml		pg/ml		pg/ml	
Control, blood alone (Con)	6.7	<5	4.6	<5	14	8	15.4	<5
Con + 50 *pg/ml* LPS	294	301	456	380	486	300	589	487
Con + BPI (1µg/ml)	<4	<5	6.9	<5	6.9	<5	8	<5
Blood with UDCA *1 mg/ml (1% ethanol)*	4.8	<5	6	6.5	<4	8.5	<4	<5
+ LPS + UDCA	<4	5.6	<4	<5	6.4	9.1	<4	<5
+ LPS + Ethanol 1% (no UDCA)	126	119	315	286	407	318	430	408
Blood with UDCA *100µg/ml (0.1% ethanol)*	10.6	<5	14	<5	42.7	46.3	16	<5
+ LPS + UDCA	114	114	41.3	20.4	49.6	306	397	419
+ LPS + Ethanol 0.1% (no UDCA)	265	230	221	263	599	375	569	414
Blood with UDCA *10 µg/ml (0.01% ethanol)*	8.5	<5	8.3	<5	13.7	9	12.3	<5
+ LPS	279	248	432	358	617	400	600	499

Figure 9: LPS - Neutralisation by UDCA in whole blood in patient 1

Measurements by Immulite	P1 / -1		P1 / 0		P1 / 1		P1 / 2		P1 / 5	
	TNF	IL6	TNFα	IL6	TNFα	IL6	TNFα	IL6	TNFα	IL6
	pg/ml		pg/ml		pg/ml		pg/ml		pg/ml	
Control, blood alone (Con) Con + 50 *pg/ml* LPS Con + BPI (1µg/ml)	28.7 878 29.7	11.2 573 < 5	70.2 938 15.1	35.2 723 < 5						
Blood with UDCA *1 mg/ml (1% ethanol)* + LPS + UDCA + LPS + Ethanol 1% (no UDCA)	< 4 < 4	12.8 10.7	10. 6.4 648	9.8 6.0 278						
Blood with UDCA *100µg/ml (0.1% ethanol)* + LPS + UDCA + LPS + Ethanol 0.1% (no UDCA)	8.5 813	7.8 153	24.5 692 886	19.7 773 580						
Blood with UDCA *10 µg/ml (0.01% ethanol)* + LPS	38.0 952	11.4 597	93.0 1013	45.7 853						
Plasma levels			9.1	26.7	8.3	28.8	< 4	20.5	5.8	28.1

Figure 10: LPS - Neutralisation by UDCA in whole blood in patient 2

Measurements by Immulite	P2 / -1		P2 / 0	
	TNFα	IL6	TNFα	IL6
	pg/ml		pg/ml	
Control, blood alone (Con)	29.0	10.5	47.5	25.6
Con + 50 *pg/ml* LPS	731	544	807	587
Con + BPI (1µg/ml)	17.0	<5	9.8	< 5
Blood with UDCA *1 mg/ml (1% ethanol)*	< 4	10.1	< 4	7.8
+ LPS + UDCA	9.7	< 5	< 4	5.4
+ LPS + Ethanol 1% (no UDCA)	569	419	540	405
Blood with UDCA *100µg/ml (0.1% ethanol)*	14.6	7.0	35.2	19.5
+ LPS + UDCA	271	343	459	391
+ LPS + Ethanol 0.1% (no UDCA)	712	546	993	788
Blood with UDCA *10 µg/ml (0.01% ethanol)*	42.4	26.2	54.1	32.0
+ LPS	712	622	744	532
Plasma levels	4.9	6.6	< 4	7.6

Figure 11: LPS - Neutralisation by UDCA in whole blood in patient 3

Measurements by Immulite	P3 / -1		P3 / 0	
	TNFα	IL6	TNFα	IL6
	pg/ml		pg/ml	
Control, blood alone (Con)	43.1	7.9	52.1	12.9
Con + 50 *pg/ml* LPS	450	378	490	346
Con + BPI (1µg/ml)	16.4	< 5	10.0	< 5
Blood with UDCA *1 mg/ml (1% ethanol)*	6.5	10.4	< 4	9.1
+ LPS + UDCA	< 4	10.3	< 4	10.7
+ LPS + Ethanol 1% (no UDCA)	208	108	288	169
Blood with UDCA *100µg/ml (0.1% ethanol)*	12.1	9.4	21.7	8.4
+ LPS + UDCA	48.0	63.5	241	382
+ LPS + Ethanol 0.1% (no UDCA)	383	285	448	346
Blood with UDCA *10 µg/ml (0.01% ethanol)*	34.7	8.0	39.4	10.7
+ LPS	375	310	468	366
Plasma level	13.0	17.1	10.2	15.9

Figure 12: LPS - Neutralisation by UDCA in whole blood in patient 4

Measurements by Immulite	P4 / -1		P4 / 0		P4 / 1		P4 / 2	
	TNFα	IL6	TNFα	IL6	TNFα	IL6	TNFα	IL6
	pg/ml		pg/ml		pg/ml		pg/ml	
Control, blood alone (Con)	34.5	10.4	29.5	10.2	4.7	< 5	4.0	< 5
Con + 50 *pg/ml* LPS	224	98.4	172.0	77.5	156	88.9	100	46.8
Con + BPI (1µg/ml)	18.1	< 5	33.5	7.1	< 4	< 5	< 4	< 5
Blood with UDCA *1 mg/ml (1% ethanol)*	< 4	8.2	< 4	8.2	< 4	< 5	< 4	8.8
+ LPS + UDCA	< 4	6.6	< 4	9.5	< 4	5.6	< 4	6.3
+ LPS + Ethanol 1% (no UDCA)	132	48.0	98.5	68.4	66.9	35.6	49.5	26.5
Blood with UDCA *100µg/ml (0.1% ethanol)*	83.7	49.6	44.5	60.0	4.2	< 5	< 4	< 5
+ LPS + UDCA	242	257	55.8	61.0	89.7	36.6	39.9	34.6
+ LPS + Ethanol 0.1% (no UDCA)	154	130	136.0	159	141	82.7	120	81.0
Blood with UDCA *10 µg/ml (0.01% ethanol)*	42.3	13.6	174	72.0	10.9	< 5	5.2	< 5
+ LPS	188	80.2	278	166	163	88.7	95.6	53.4
Plasma levels	8.1	< 5	< 4	< 5	< 4	< 5	4.7	< 5

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Auker 11 #5

Norris, McLaughlin & Marcus, P.A.

220 East 42nd Street, 30th Floor
New York, NY 10017

If each inventor understands English, the Declaration and Power of Attorney below is suitable for use when filing a regular patent application and also when entering the national stage, in the case of an International application designating the USA under the PCT.

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION	Attorney Docket No. 101195-

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name,
I believe I am the original, first and sole inventor (if only one name is listed below at 201) or an original, first and joint inventor (if plural names are listed below at 201-210) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Therapy and Use of Compounds in Therapy

the specification of which (check one)

____ is attached hereto

__✓__ was filed on _____9 March 2000____

under Serial Number __PCT/EP00/02062_____ and was amended on _____
(if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I list below any prior foreign application(s) for patent or inventor's certificate in respect of which foreign priority benefits are claimed under 35 USC 119; and any prior foreign application(s) for patent or inventor's certificate in respect of which such foreign priority rights are not claimed and which has a filing date before that of any application in respect of which such foreign priority benefits are claimed:

Application Number	Country	Filing Date (day, month, year)	Priority Claimed under 35 USC 119
9905315.9	**Great Britain**	**9 March 1999**	YES:_✓__ NO:___
9905300.1	**Great Britain**	**9 March 1999**	YES:_✓__ NO:___
9905310.0	**Great Britain**	**9 March 1999**	YES:_✓__ NO:___
9905307.6	**Great Britain**	**9 March 1999**	YES:__✓__ NO:___
9905314.2	**Great Britain**	**9 March 1999**	YES:__✓__ NO:___

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

Application No.	Filing Date

Combined Declaration and Power of Attorney
101195- .
Page 2

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transmit all business in the Patent and Trademark Office connected therewith:

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208	Family Name	First Given Name	Second Given Name
	City of Residence	State or Foreign Country	Country of Citizenship
	Post Office Address	City	State & ZIP/Country
209	Family Name	First Given Name	Second Given Name
	City of Residence	State or Foreign Country	Country of Citizenship
	Post Office Address	City	State & ZIP/Country

210	Family Name	First Given Name	Second Given Name
	City of Residence	State or Foreign Country	Country of Citizenship
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Signature of Inventor 202	Date 28/11/01
Signature of Inventor 203	Date
Signature of Inventor 204	Date
Signature of Inventor 205	Date
Signature of Inventor 206	Date
Signature of Inventor 207	Date
Signature of Inventor 208	Date
Signature of Inventor 209	Date
Signature of Inventor 210	Date

210	Family Name	First Given Name	Second Given Name
	City of Residence	State or Foreign Country	Country of Citizenship
	Post Office Address	City	State & ZIP/Country

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 201	Date 27/11/01
Signature of Inventor 202	Date 28/11/01
Signature of Inventor 203	Date 26/01/02
Signature of Inventor 204	Date
Signature of Inventor 205	Date
Signature of Inventor 206	Date
Signature of Inventor 207	Date
Signature of Inventor 208	Date
Signature of Inventor 209	Date
Signature of Inventor 210	Date

210	Family Name	First Given Name	Second Given Name
	City of Residence	State or Foreign Country	Country of Citizenship
	Post Office Address	City	State & ZIP/Country

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 201	Date 27/11/01
Signature of Inventor 202	Date 28/11/01
Signature of Inventor 203	Date
Signature of Inventor 204 x	Date x 20/12/01
Signature of Inventor 205	Date
Signature of Inventor 206	Date
Signature of Inventor 207	Date
Signature of Inventor 208	Date
Signature of Inventor 209	Date
Signature of Inventor 210	Date

210	Family Name	First Given Name	Second Given Name
	City of Residence	State or Foreign Country	Country of Citizenship
	Post Office Address	City	State & ZIP/Country

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 201	Date 27/11/01
Signature of Inventor 202	Date 28/11/01
Signature of Inventor 203	Date
Signature of Inventor 204	Date
Signature of Inventor 205	Date 18/12/01
Signature of Inventor 206	Date
Signature of Inventor 207	Date
Signature of Inventor 208	Date
Signature of Inventor 209	Date
Signature of Inventor 210	Date

210	Family Name	First Given Name	Second Given Name
	City of Residence	State or Foreign Country	Country of Citizenship
	Post Office Address	City	State & ZIP/Country

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 201	Date 27/11/01
Signature of Inventor 202	Date 28/11/01
Signature of Inventor 203	Date
Signature of Inventor 204	Date
Signature of Inventor 205	Date
Signature of Inventor 206	Date 21.1.02
Signature of Inventor 207	Date
Signature of Inventor 208	Date
Signature of Inventor 209	Date
Signature of Inventor 210	Date